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Short Communication

Primapterinuria: A Clinical Update

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Introduction

Primapterinuria is the recently discovered variant of hyperphenylalaninemia characterized by the excretion of 7-substituted pterins in the patients urine (1). Primapterinuria differs from the classical PKU and other variants of tetrahydrobiopterin deficiency because these patients do not need treatment with a low-phenylalanine diet or with neurotransmitter precursors L-DOPA and 5-hydroxytryptophan. The first patients were described by Dhondt et al. (2) and Blaskovics & Giudici (3). A loading test with tetrahydrobiopterin was the first indication that primapterin (7-biopterin) may derive from 6-biopterin (4). Tetrahydrobiopterin, dihydrobiopterin and sepiapterin given orally resulted in a significant increase in 6- and 7-substituted biopterin, and the ratio remained the same (1.0 to 1.5) after loading (5). From *in vitro* experiments it is known that primapterin can be formed during the phenylalanine-4-hydroxylase reaction in a pterin-4a-carbinolamine dehydratase free system (6). To the present time all known enzymes involved in the biosynthesis or regeneration of tetrahydrobiopterin have been found to be normal in these patients and a pterin-4a-carbinolamine dehydratase deficiency has been proposed (Fig. 1).

Results and Discussion

Nine patients with this new disorder in the regeneration of tetrahydrobiopterin are now known. The infants initially present with variably elevated plasma phenylalanine (Phe) levels and are recognized in newborn screening programs. The Phe levels may rise to the 25 to 35 mg% range. If started on a low-Phe diet the Phe levels fall rapidly and Phe often needs to be quickly replaced. Phe levels gradually decrease over

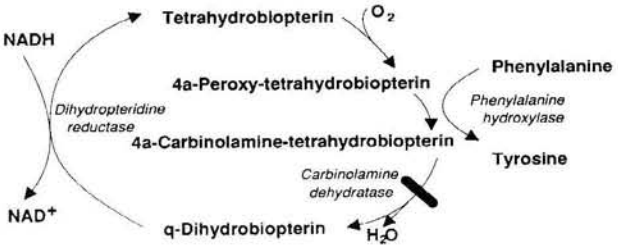

Figure 1. Phenylalanine-4-hydroxylase regenerating system and possible defect in primapterinuria.

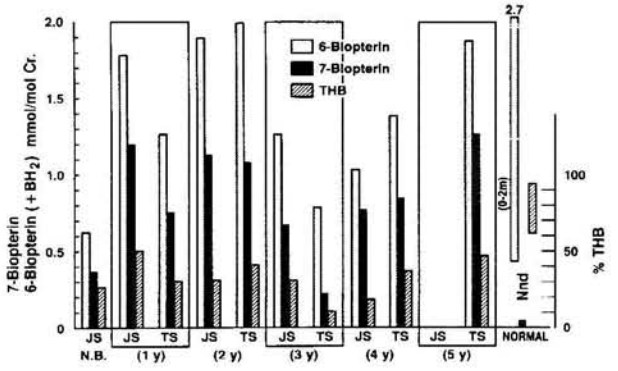

Figure 2. 6-Biopterin, 7-biopterin (primapterin) and tetrahydrobiopterin (THB) in two children with primapterinuria at different ages. %THB of the sum of all biopterins.
N. B. = newborn

time to normal regardless of dietary Phe intake. Seven of the affected children are now on normal diets and Phe levels are in the normal range; the two others are moving in that direction. These infants and children would fall into the category of transient hyperphenylalaninemia/phenylketonuria unless they are identified by their urinary pterin profile. The only physical clinical findings of note have been transiently variable muscle tone, either hyper or hypo. In all instances, to the present time, the condition appears to be benign.

All measurable substrates related to normal functioning have been present. The known phenylalanine hydroxylating system enzymes measured appear to be normal; however, phenylalanine-4-hydroxylase and pterin-4a-carbinolamine dehydratase, per se, have not been measured. The persisting abnormalities appear to be subnormal levels of tetrahydrobiopterin and elevated levels of primapterin (Fig. 2). It would appear that primapterin or its tetrahydro form has some effect on phenylalanine-4-hydroxylase.

Acknowledgement

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